Medications for Weight Loss

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Executive Summary

It comes as no surprise that achieving and maintaining a healthy weight improves the overall health and wellness of an individual. Excess body weight may lead to an array of comorbid conditions (**Table 1**). The prevalence of obesity in the United States has steadily increased in the last few decades and is a major health and economic concern. The primary cause of being overweight or obese is the imbalance between caloric intake and energy output. Factors such as genetics, presence of chronic diseases and certain medications are known to impact weight gain. The following overview will focus on the pharmacologic treatment options used to treat adult patients who are overweight or obese.

Acronyms	
BMI	Body mass index
CNS	Central nervous system
CV	Cardiovascular
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
MACE	Major adverse cardiovascular events
T2DM	Type 2 diabetes

Key Takeaways

1. Lifestyle interventions such as dietary modification, exercise, and behavioral therapy are recommended as first- line treatment options for weight management.
2. Weight loss pharmacotherapy has been proven to be effective when used in combination with a healthy lifestyle.
3. Medications used alone (without behavioral and lifestyle modifications) have not proven to be effective at achieving and maintaining weight loss.
4. At this time, drugs approved for weight management utilized weight were done so based off the surrogate endpoint of weight loss. It is still too early to conclude that GLP-1 agonists improve CV related outcomes in the non-diabetic obese population. GLP-1 agonist research evaluating CV related outcomes in the non-diabetic obese population is currently on-going.

Table 1: Weight-related Comorbidities

T2DM	Metabolic disease
Hypertension	Cardiovascular disease
Dyslipidemia	Mental illness (anxiety, depression, etc.)
Stroke	Gallbladder disease
Osteoarthritis	Certain types of cancers
Sleep apnea	

Table 2: The Centers for Disease Control and Prevention (CDC) Overweight and Obesity Classification [2]

Classification	Body mass index (BMI)
Overweight	25 kg/m^2 to 29.9 kg/m^2
Obesity	
Class 1:	30 kg/m^2 to < 35 kg/m^2
Class 2:	35 kg/m^2 to < 40 kg/m^2
Class 3 or severe obesity:	BMI of ≥ 40 kg/m^2 or ≥ 35 kg/m^2 plus the presence of a weight related comorbidity

Weight loss as little as 5% of total body weight has been shown to improve weight-related comorbidities. Treatment of weight management consists of lifestyle modifications, surgical interventions and pharmacotherapy ([1]). Multiple societal organizations have published clinical practice guidelines for the management and treatment of obesity. These organizations all agree that lifestyle interventions such as diet, exercise and behavioral modifications should be the first

step for anyone seeking to lose weight. Pharmacotherapy may be considered when a patient reaches a BMI of ≥ 30 kg/m^2 or 27 mg/m^2 plus at least one comorbid medical condition (e.g., hypertension, dyslipidemia, T2DM and obstructive sleep apnea). Bariatric surgery becomes an option when a patients reaches a BMI of ≥ 40 kg/m^2 or ≥ 35 kg/m^2 plus a comorbidity. [(3,4,5)]

FDA-approved medications for weight management work by one of the following mechanisms: reducing caloric intake by appetite suppression, promoting energy output by CNS stimulation or inhibiting intestinal calorie absorption. Although medications indicated for weight loss have been shown to be effective when used in combination with lifestyle modifications, it is unclear if their effectiveness is maintained in the absence of such lifestyle changes. It is important that providers consider the patient's current comorbidities and motivation to lose weight prior to therapy initiation.

Medications approved for weight loss can be divided into two different groups: agents categorized for short-term management (12 weeks) or chronic management. Agents approved for short-term management work by stimulating the CNS and thus promoting caloric expenditure (**Table 3**). Long-term use of these agents is not recommended because of possible adverse cardiovascular risks and addiction potential. There are currently five medications approved for chronic management (**Table 4**). These medications have become more favorable due to their improved safety profile, effectiveness in achieving weight loss and provider comfort level. Pharmacologic treatment for obesity is considered effective if weight loss is ≥5% of total body weight at three months in the absence of medication-related adverse effects.

Agents recommended for the short-term management of weight loss entered the market in the 1980s and are now all available as generic formulations (**Table 3**). Historically, it was believed that obesity could be treated and cured with a short-term approach. Because of this historic mindset, clinical trials were designed to evaluate short-term efficacy. Results from a meta-analysis evaluating the efficacy of benzphetamine, diethylpropion, phentermine and orlistat compared to placebo revealed a 2 kg to 4 kg difference in weight loss with no agent having a clear advantage over another[(8)].

Table 3: Medications for Short-Term Management of Obesity

Medication	Mechanism	Dose	Cost ($-$$$)
Amphetamine (Evekeo)	Appetite suppression and increased energy output	5-10 mg TID	$
Benzphetamine (Didrex)	Appetite suppression and increased energy output	25-50 mg TID	$
Diethylpropion (Tenuate, Dospan)	Appetite suppression and increased energy output	25 mg TID	$
Phendimetrazine (Bontril PDM)	Appetite suppression and increased energy output	35 mg TID	$
Phentermine (Adipex-P,Lomaira)	Appetite suppression and increased energy output	15-30 mg QD	$

Medications within the GLP-1 agonist class have reignited interest for the pharmacologic treatment of weight management. Saxenda® (liraglutide) and Wegovy™ (semaglutide) are two GLP-1 agonist agents which currently have weight loss indications. Wegovy was approved on June 4, 2021, as an adjunct to diet and exercise for chronic weight management in adults with a BMI of ≥ 30 kg/m2 or 27 mg/m2 plus at least one weight-related comorbidity.

Wegovy offers a once-weekly administration advantage over Saxenda's once-daily administration. These products are effective at helping those with T2DM control their diabetes and lose weight [11,12]. It is worth mentioning that Mounjaro™ (tirzepatide) was approved on May 13, 2022, for the treatment of T2DM and is currently being evaluated for a weight loss indication. Mounjaro is a novel duel-action product that acts on GIP and GLP-1 receptors [13].

GLP-1 agonists are titrated gradually (weekly to monthly depending on the product) to target a maximum dose or maximum tolerated dose (whichever comes first) in order to minimize the gastrointestinal adverse effects. Although gastrointestinal adverse effects occur frequently for the GLP-1 agonist class, they are typically mild and are easily managed by slowing the titration phase or reducing the dose. GLP-1 agonists are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 [9,10].

GLP-1 agonists have proven to reduce MACE in those with T2DM and established CV disease. At the time of this document's creation, ongoing research is evaluating Wegovy's effect on MACE in nondiabetic obese people with established CV disease.

Table 4: Medications for the Chronic Management of Obesity

Medication	Mechanism	Dose	Cost	Prescriber Pearls
Contrave® (naltrexone/bupropion ER)	Appetite regulation and craving reduction	2 tablets (8 mg/90 mg) BID	$$	• Oral and twice daily dosing • Black box warning and numerous contraindications
Qsymia® (phentermine/topiramate ER)	Appetite regulation and satiety enhancement	1 tablet (15mg/92mg) daily	$$	• Oral and once daily dosing • Numerous contraindications • C-IV controlled substance • REMS – risk of birth defects
Saxenda® (liraglutide)	Appetite regulation; GLP-1 receptor agonist	3 mg SC daily	$$$	• SQ administration, dosed once daily, titrated weekly • Approved for individuals 12 and older • Consider for overweight T2DM patients • Rebound weight gain expected if discontinued • Expect high rates of gastrointestinal adverse effects such as abdominal pain and nausea
Wegovy™ (semaglutide)	Appetite regulation; GLP-1 receptor agonist	2.4 mg SC weekly	$$$	• SQ administration, dosed once weekly, titrated monthly • Consider for overweight T2DM patients • Rebound weight gain expected if discontinued • Expect high rates of gastrointestinal adverse effects such as abdominal pain and nausea
Xenical® (orlistat)	Inhibition of dietary fat absorption	120 mg TID	$$	• Oral administration three times daily before meals • Lower strength available OTC • Several contraindications • High rates of abdominal pain, defecation urgency, flatulence, and anal discharge

Table 5 lists the comparative efficacy for the various agent approved for chronic weight management in adults. It is important to keep in mind that these agents have not been studied head-to-head which makes cross-trial comparison difficult. The following table shows comparative data expressed in ranges to incorporate results from multiple randomized, double-blind, placebo-controlled studies [13].

Table 5: Comparative Efficacy of Chronic Weight Management Medications in Adults

	Duration of Treatment (weeks)	Mean % Decrease in Body Weight from Baseline	% of Participants with ≥5% Weight Loss	% of Participants with >10% Weight Loss	Mean Decrease in Waist Circumference (cm)
Contrave	56	3.7%-8.1%	36%-57%	15%-35%	6.2-10
Qsymia	52	9.8%-10.9%	67%-70%	47%-48%	9.2-10.9
Saxenda	56	5.4%-7.4%	49%-62.3%	22.4%-33.9%	6-8.2
Wegovy	68	9.6%-16%	67.4%-84.8%	44.5%-73%	9.4-14.6
Xenical	52	-	35.5%-54.8%	16.9%-24.8%	-

Data indicates that pharmacotherapy is effective for weight loss when combined with dietary modifications, exercise, and behavioral therapy. The question that remains to be answered is "Does pharmacotherapy alone lead to weight loss and more importantly improve comorbid conditions associated with being overweight?" When a patient meets the diagnostic criteria to start pharmacotherapy, it is important for the managing provider to consider the following: the patient's motivation to lose weight, comorbidities, knowledge of a healthy lifestyle and supporting resources before starting therapy. Also, it is important to weigh medication efficacy and safety before drug selection. Like most other chronic diseases, lifestyle modifications remain the cornerstone of treatment and are recommended first-line. Patients who do not respond to these interventions may be considered for medication therapy.

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Complications Related to Bariatric Surgery – Nutritional Deficiencies and Dumping Syndrome

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Executive Summary

Bariatric surgery may result in significant weight loss and improvements in metabolism. Nutritional deficiencies are common and are affected by the type of surgery performed. Deficiencies are more common following malabsorptive surgery (BPD/DS and RYGB) compared to restrictive procedures (SG and LAGB). Guidelines recommend postoperative multivitamin supplementation, however long term adherence to multivitamin supplementation is generally considered to be poor. Decrease in adherence results in nutritional deficiencies and should be reinforced through primary care.

Gastrointestinal changes in physiology may result in dumping syndrome in an estimated 20% to 50% of patients (early dumping syndrome). Late dumping syndrome is now referred to as PHH and occurs in 0.1% to 0.3% of patients. Both can be treated with dietary interventions, however pharmacotherapy can be utilized when dietary changes fail to achieve symptom resolution.

Acronyms	
ACOG	American College of Obstetricians and Gynecologists
BID	*Bis in die*, twice a day
BPD/DS	Biliopancreatic diversion/duodenal switch
IM	Intramuscular
LAGB	Laparoscopic adjust gastric band
LAR	Long-acting release
MOA	Mechanism of action
MVT	Multivitamin
PHH	Postprandial hyperinsulinemic hypoglycemia
RYGB	Roux-en Y gastric bypass
SG	Sleeve gastrectomy
SQ	Subcutaneous
TID	*Ter in die*, three times a day

Key Takeaways

- MVT supplementation is necessary following bariatric surgery and nutritional deficiencies are affected by type of surgery.
- Non-adherence to MVT supplementation may be related to complex dosing regimens, cost, pill burden, and adverse effects and may lead to nutritional deficiencies.
- If dietary interventions for dumping syndrome are not effective, pharmacotherapy can be explored, including octreotide for early dumping syndrome, and nifedipine, acarbose, diazoxide, or octreotide for late dumping syndrome/PHH.

MVT supplementation following bariatric surgery significantly increases pill burden and frequency of medication dose administration in order to prevent nutritional deficiencies. Drug-drug interactions can also occur between MVT supplements as well as between chronic medications and MVT supplements. There are specially formulated MVTs that contain the recommended doses of nutrients needed following bariatric surgery, however these come at an added cost to the patient and are typically more expensive than other MVT supplements. All of these factors can contribute to decreased adherence which may result in nutritional deficiencies. **Table 1** outlines supplementation recommendations to help prevent nutrient deficiencies following weight loss surgery.

Table 1: Supplementation Recommendations to Help Prevent Nutrient Deficiencies

Supplement	Dosing	Considerations
Vitamin B1 (Thiamine)	• 50 mg dose of thiamine from a B-complex supplement once or twice daily	• Take with food • May cause nausea, mostly well tolerated
Vitamin B12 (Cyanocobalamin)	• Oral → 350-500 mcg daily • Parenteral (IM or SQ) → 1000 mcg monthly	• Take with food • May cause headache, mostly well tolerated

Folate (Folic Acid)	• 400-800 mcg daily from MVT • Women of childbearing age: 800-1000 mcg daily	• May cause nausea, bloating, gas, bitter taste, irritability, trouble sleeping • May interact with some chemotherapy drugs, anticonvulsants, and green tea extract (consult pharmacist for interaction management)
Iron (Ferrous Sulfate)	• 18 mg daily from MVT (males and patients without history of anemia) • 45-60 mg elemental iron daily (menstruating females and patients who have undergone RYGB, SG, or BPD/DS)	• May cause darkening of stools, abdominal pain, heartburn, nausea, vomiting, and diarrhea • Iron supplements should be taken in divided doses separated from calcium supplements, acid reducing medications, and food high in phytates or polyphenols • Separate by one hour from oral bisphosphonates • May interact with some antivirals, quinolones, tetracyclines, and levothyroxine – separate administration times

Calcium	• BPD/DS → 1800-2400 mg daily
	• RYGB → 1200-1500 mg daily
	• SG → 1200-1500 mg daily
	• LAGB → 1200-1500 mg daily
		• To enhance calcium absorption:
		  ○ Calcium should be given in divided doses
		  ○ Calcium carbonate should be taken with meals
		  ○ Calcium citrate may be taken with or without meals
		  ○ Calcium should be taken with full glass of water (8 oz)
		• Separate calcium 2 hours from other medications
		• May cause upset stomach and diarrhea

Vitamin D	• 3000 IU of cholecalciferol (vitamin D3) daily to maintain 25(OH)D level >30 ng/mL • If 25(OH)D level is <30 ng/mL: may require higher doses of D3 or 50,000 IU of ergocalciferol (vitamin D2) 1-3 times per week	• May cause nausea, constipation, muscle aches or stiffness
Vitamin A	• BPD/DS → 10,000 IU daily • RYGB → 5,000-10,000 IU daily • SG → 5,000-10,000 IU daily • LAGB → 5,000 IU daily	• May cause birth defects if large doses are taken during pregnancy – ACOG recommends no more than 5,000 IU daily
Vitamin E	• 15 mg daily	N/A
Vitamin K	• BPD/DS → 300 mcg daily • RYGB → 90-120 mcg daily • SG → 90-120 mcg daily	• Interacts with warfarin

	• LAGB → 90-120 mcg daily	• May cause allergic reactions, blue lips skin or fingernails, sudden headache, dizziness, or fainting
Zinc	• BPD/DS → 16-22 mg daily • RYGB → 8-22 mg daily • SG → 8-11 mg daily • LAGB → 8-11 mg daily	• Take on an empty stomach with plain water, at least 1 hour before or 2 hours after a meal • May cause upset stomach and heartburn • May interact with copper and some antibiotics
Copper	• BPD/DS → 2 mg daily • RYGB → 2 mg daily • SG → 1 mg daily • LAGB → 1 mg daily	• A ratio of 1 mg copper has been recommended for every 8 to 15 mg of elemental zinc to prevent copper deficiency

Early Dumping Versus Postprandial Hyperinsulinemia Hypoglycemia

Early Dumping Syndrome: Occurs 10 to 30 minutes after a high carbohydrate meal resulting in rapid emptying of food into the small bowel. This occurs due to hyperosmolality of food and rapid shifts from the plasma to the bowel, resulting in sympathetic nervous system response. Symptoms usually present as colicky abdominal pain, diarrhea, nausea and tachycardia. First-line treatment is dietary intervention. Octreotide can be used in severe cases that do not respond to dietary changes. Octreotide administered SQ TID or octreotide LAR administered monthly can both reduce symptoms and improve quality of life.

PHH: Previously referred to as late dumping syndrome. Most commonly appears post-RYGB and is a rare complication typically presenting 1-5 years after surgery. The pathophysiology of PHH is not well known but is thought to be due to an altered GLP-1 response and increased insulin post-meal. Dietary intervention is recommended as first-line treatment, but patients refractory to diet adjustment can be treated with pharmacotherapy. There are currently no FDA-approved medications for treatment of PHH, however case reports have shown several agents to be effective either used alone or in combination. **Table 2** outlines pharmacotherapy for treatment of PHH.

Table 2: Pharmacotherapy for Treatment of PHH

Medication	MOA	Dosing
Nifedipine	Reduces insulin secretion	30 mg/day
Acarbose	Reduces postprandial blood glucose increment and insulin response	25 – 100 mg PO with meals
Diazoxide	Reduces insulin release	50 mg PO BID
GLP-1 receptor antagonist	Block the action of GLP-1 which can suppress postprandial insulin secretion	*Investigational drug*
Octreotide	Reduces insulin and glucagon secretion	100 mcg SQ BID

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Pharmacotherapy Considerations: Agents That Cause Weight Gain

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Executive Summary

Many factors contribute to the development of obesity; unfortunately, a number of medications can be a contributing factor. As a rule of thumb, if an alternative is not available, consider using the lowest effective dose of the medication for the shortest amount of time. **Table 1** lists medications associated with weight gain as well as the extent of weight gain and alternatives therapies.

Acronyms	
ARB	Angiotensin II receptor blocker
BMI	Body mass index
DNRI	Norepinephrine – dopamine reuptake inhibitor
GLP-1	Glucagon-like peptide 1
MAOI	Monoamine Oxidase Inhibitors
SGLT2	Sodium-glucose co-transporter-2
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SU	Sulfonylureas
TCA	Tricyclic antidepressant
TeCAs	Tetracyclic antidepressant
TZD	Thiazolidinediones

Overview of Medications That Cause Weight Gain

The amount and mechanism behind weight gain varies by agent. Common mechanisms include appetite stimulation, fat accumulation, decreased basal metabolic rate, fluid retention and impaired exercise tolerance.

Diabetic Medications

- Insulin functions as an anabolic hormone; it promotes the accumulation of glucose, fat and protein.
- TZDs cause weight gain through mechanisms of both fluid retention and fat accumulation.
- SUs stimulate insulin release from the pancreas. SUs are considered to cause less weight gain than insulin and similar weight gain to TZDs.
- Metformin and SGLT2 inhibitors provide modest weight loss effects (2-4 kg). GLP-1 agonists provide the most weight loss effects and should be considered as a viable form of treatment in obese diabetic patients[1].

Antidepressants

- TCAs are well known for having unwanted anticholinergic side effects in addition to weight gain. TCA blockade of histamine, serotonin and peripheral alpha receptors results in patients having increased carbohydrate cravings and slowed basal metabolic rates.
- Mirtazapine is a TeCAs with more alpha-2 antagonist activity. It has a similar side effect profile with TCAs but less weight gain.[2]
- SSRI paroxetine displays the greatest weight-promoting effect[3]. Other SSRIs like fluoxetine and sertraline display initial weight loss and followed by more weight gain with chronic use[4].

Antipsychotics

- In general first-generation antipsychotics are associated with lower rates of weight gain than atypical antipsychotics[5].
- Aripiprazole and ziprasidone are associated with the least amount of weight gain[5].
- Lithium causes weight gain through fluid retention and secondary to decreased metabolic rate from hypothyroidism.

Anticonvulsants

- Most anticonvulsant weight gain is attributed to water retention and appetite stimulation.
- Gabapentin and pregabalin display a positive correlation between dose and weight gain.

Steroid Hormones

- Acute use of corticosteroids do not appear to result in significant weight gain. However, chronic steroid therapy can result in significant weight gain, due in part to reduced glucose tolerance leading to an increase in fat accumulation[6,7].
- At this time, there is no consensus on contraceptive use and weight gain. There is a scarcity of randomized controlled clinical trials, and the variety of contraceptive formulations makes comparing these studies problematic. Four placebo-controlled trials have been conducted with combination contraceptives (e.g., estrogen with progestin). These trials failed to demonstrate a link between combination contraceptives and weight gain[8].
- Women with comorbid conditions or BMI > 30 may benefit from using oral formulations over injectable formulations[9].

Antihistamines

- Antihistamine blockade induces sedative effects as well as appetite stimulation.
- First-generation agents such as diphenhydramine are more likely to display weight gain effects than second-generation agents such as cetirizine due to their more potent CNS activity[10].

Alpha/Beta-Adrenergic Blockers

- Blockage of the beta-adrenergic receptors induces a reduction in the basal metabolic rate[9].
- Beta – blockers with peripheral vasodilation action such as carvedilol, labetalol or nebivolol seem to display lower rates of weight gain[9].

Table 1: Medications That Cause Weight Gain

Drug Class	Common Name (Brand Name)	Approximate Weight Gain	Alternative Pharmacotherapy (Weight Neutral or Weight-Loss*) Note: list is not all-inclusive
Diabetes Therapies			
Insulin *Most weight gain occurs during the first three months of use*	insulin lispro (Humalog) insulin aspart (Novolog) insulin glulisine (Apidra)	Weight gain differs with type and regimen used [11] Basal regimen: ~4 kg Biphasic regimen: ~6 kg Prandial regimen: ~7 kg	Metformin (Glucophage)* **GLP-1 Agonist**: Dulaglutide (Trulicity)* Semaglutide (Ozempic)*
TZDs	Pioglitazone (Actos)	~2.6 kg over 30 days [12]	**SGLT-2 inhibitors**: * Alpha-glucosidase

SUs	Glipizide (Glucotrol) Glyburide (Glynase) Glimepiride (Amaryl)	~2.2 kg after 30 days[12] ~2.6 kg after 30 days[12] ~2.1 kg after 30 days[12]	Inhibitors* Acarbose (Precose) Miglitol (Glyset) **Dipeptidyl peptidase-4 inhibitor:** Saxagliptin (Onglyza) Sitagliptin (Januvia) Linagliptin (Tradjenta)
Psychiatric Therapies			
TCAs	Amitriptyline (Elavil) Nortriptyline (Pamelor) Doxepin Imipramine (Tofranil) Trimipramine (Surmontil) Mirtazapine (Remeron)	~1.5 – 2.4 kg over 12 weeks [13] ~ 1.7 – 2.6 kg over 12 weeks[13]	**SNRI:** Venlafaxine (Effexor XR)* Desvenlafaxine (Pristiq)* **DNRI:** Bupropion (Wellbutrin, Zyban)*
MAOIs	Phenelzine (Nardil)	~20 kg over 4 months[14]	
SSRIs	Paroxetine (Paxil) Citalopram (Celexa) Fluoxetine (Prozac, Sarafem) Sertraline (Zoloft) Fluvoxamine (Luvox CR)	Initial weight-loss followed by gain within 6 months in a minority of patients	
Lithium	(Eskalith, Eskalith CR, Lithobid)	~ 1 – 10 kg[4]	
Antipsychotics *First-generation agents tend to cause less weight gain than atypicals*	**First-Generation:** Chlorpromazine **Atypical:** Clozapine (Clozaril) Risperidone (Risperdal) Olanzapine (Zyprexa) Quetiapine (Seroquel)	~0.55 kg over 4-12 weeks[15]	Aripiprazole (Abilify) Ziprasidone (Geodon)* Haloperidol (Haldol)
Anticonvulsants	Carbamazepine (Equetro) Gabapentin (Neurontin) Pregabalin (Lyrica) Valproate (Depakote)	~ 1.5 kg over six months[9] ~ 2.2 kg over 1.5 months[9] ~ 5.2 kg over 2 years in diabetic patients[9] ~2 kg over one year[9]	Lamotrigine (Lamictal)* Topiramate (Topamax)* Zonisamide (Zonegran)* Levetiracetam

Steroid Hormones			
Oral Corticosteroids	Prednisone	~ 2 kg over 24 weeks[16] ~ 5 kg over one year[17]	NSAIDs were applicable Avoid chronic use
Other Therapies			
Antihistamines	Diphenhydramine Cetirizine	~ 1 kg over 3 weeks[18]	Decongestants, Steroid inhalers
Alpha/Beta-Adrenergic Blockers *carvedilol, nebivolol are thought to be weight neutral*	Propranolol (Inderal) Metoprolol (Lopressor, Toprol XL) Atenolol (Tenormin)	3 kg over 24 months[19] 0.6 kg over 24 months[19]	**ACE Inhibitors:** Ramipril (Altace) Benazepril (Lotensin) Enalapril (Vasotec) Lisinopril (Prinivil, Zestril) **ARBs:** Losartan (Cozaar) Candesartan (Atacand) **Ca^{+2} Channel Blockers:** Amlodipine (Norvasc)

NOTE: This list is not all-inclusive. When comparing weight gain between specific agents or drug classes, keep in mind that the data in this chart were selected from various sources and there may be variability in study design, patient characteristics, indication for treatment, length of therapy, etc.

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Medication Use After Bariatric Surgery - Management for Chronic Conditions

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Executive Summary

Obesity is a significant factor in the incidence of chronic diseases in adults such as diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, metabolic diseases, chronic kidney disease, obstructive sleep apnea, osteoarthritis and many others. Bariatric surgeries are indicated in patients with a BMI > 40 kg/m^2, and those with a BMI >35 kg/m^2 (>25 kg/m^2 for Asians) with comorbid conditions that are not controlled with medication and lifestyle management alone. Bariatric surgeries cause alteration in the gastrointestinal tract, changing the way patients metabolize both food and medications. This synopsis provides an overview of the management of chronic conditions following bariatric surgery.

Key takeaways:

- Insulin secretagogues, SGLT-2 Inhibitors and TZD should be discontinued prior to surgery.
- Consider CGM following surgery to assess glycemic control, glycemic response to weight loss, and monitor for hypoglycemia.
- Continue hyperlipidemia and hypertension treatment following surgery, monitor response to weight loss.
- NSAIDs are contraindicated following surgery due to increased risk of GI bleeds and ulceration.

Acronyms	
BG	Blood glucose
BMI	Body mass index
CGM	Continuous glucose monitor
ER	Extended release
GI	Gastrointestinal
HBA1C	Glycated hemoglobin
HTN	Hypertension
NSAID	Nonsteroidal anti-inflammatory drug
SGLT-2	Sodium-glucose cotransporter-2
TSH	Thyroid-stimulating hormone
TZD	Thiazolidinedione

Managing Diabetes in Post-bariatric Surgery Patients

- Bariatric surgery achieves superior glycemic control for at least 5-15 years and reduction of cardiovascular risk in patients with type 2 diabetes and obesity compared with nonsurgical weight loss strategies due to the important role the GI tract plays in glucose homeostasis.
- It reduces all-cause mortality, reduces the incidence of microvascular disease, improves quality of life, decreases cancer risk, and improves cardiovascular disease risk factors and long-term cardiovascular events in type 2 diabetic patients.
- HBA1C should be followed to evaluate need for continued antidiabetic pharmacologic therapy.
- All insulin secretagogues, SGLT-2 inhibitors and TZDs should be discontinued prior to surgery and not restarted post-operatively, to decrease the risk of hypoglycemia.
  - Insulin Secretagogues
    - Sulfonylureas: glipizide, glimepiride, glyburide
    - Meglitinides: nateglinide, repaglinide
  - SGLT-2 inhibitors: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance)
  - TZDs: pioglitazone, rosiglitazone
- The patients who have discontinued use of anti-diabetic medications must be monitored for the recurrence of hyperglycemia.
  - Continue blood glucose monitoring, adjust frequency of testing based on results.
  - Assess A1c every 3-6 months for those with persistent diabetes and at least yearly for those in remission.
  - Consider use of CGM to help determine remission and guide medication therapy.
- Besides metformin and incretin-based therapies, antidiabetic medications should be withheld if no evidence of hyperglycemia is present.

- Metformin and/or incretin-based therapies may be continued post-op in patients with type 2 diabetes until prolonged clinical resolution of type 2 diabetes is demonstrated by normalized glycemic targets – fasting, postprandial BG and HBA1c.

Post-bariatric Hypoglycemia

- Patients are at an increased risk of hypoglycemia due to:
  - Altered gastric emptying of ingested nutrients, leading to rapid intestinal glucose absorption and excessive postprandial secretion of glucagon-like peptide 1 and other gastrointestinal peptides.
  - Overstimulation of insulin release.
  - Sharp drop in plasma glucose occurs 1-3 hours after a high-carbohydrate meal.
- Post-bariatric surgery hypoglycemia may severely impact quality of life for the patient. It typically presents over a year after the surgery.
- Discontinue use of insulin secretagogues, SGLT-2 inhibitors and TZDs.
- Insulin doses should be adjusted post-op to avoid hypoglycemia.
- Patients with type 2 diabetes after bariatric surgery benefit from the use of CGM to monitor for hypoglycemia.

Hyperlipidemia

- Do not stop cholesterol medications – lipid evaluation recommended every 6-12 months based on risk and therapy.
- Need for lipid-lowering medications should be periodically evaluated by monitoring serum lipids and cholesterol levels.
- Effect of weight loss on dyslipidemia is variable and incomplete; therefore, lipid-lowering medications should not be stopped unless clearly indicated.
- Simvastatin's absorption site is not known, but it must be hydrolyzed to its active form in the stomach. Other agents should be considered to avoid this potential problem.

Hypertension

- Do not stop HTN medications – assess need for antihypertensive therapy with each visit.
- Routinely measure blood pressure at every postoperative visit to monitor blood pressure response to weight loss and evaluate need for continued antihypertensive pharmacologic therapy. Home blood pressure monitoring is also recommended to detect white coat hypertension and/or trends.
- Effect of weight loss on blood pressure is variable, incomplete, and at times transient. Medications should not be stopped unless clearly indicated; however, dosage may need to be titrated downward as blood pressure improves.
- The ACE-inhibitor enalapril is a prodrug hydrolyzed to the active form enalaprilat in the stomach, and it is absorbed in the small intestine. After bariatric surgery, its activity may decrease due to this. Other ACE-inhibitors are recommended for the treatment of hypertension.

Patients on Thyroid Hormone Replacement or supplementation

- TSH levels should be monitored frequently and medication dosing should be adjusted.
- Obesity is associated with increased TSH levels. TSH levels can decrease following bariatric surgery and weight loss.
- Dose reductions of thyroid medications may be necessary following bariatric surgery due to weight loss.
- Oral liquid forms of levothyroxine should be considered in patients with difficulty swallowing tablets after bariatric procedures.
- Oral liquid or softgel forms of levothyroxine should be considered in patients with significant malabsorption in whom adequate TSH suppression to normal ranges is difficult after bariatric procedures.

Chronic Medications to Avoid Following Bariatric Surgeries

- NSAIDs
  - Contraindicated after bariatric surgeries due to their potential to cause anastomotic ulcerations, perforations, and leaks with long-term use. Alternative pain medications should be identified prior to the surgery.
  - Acetaminophen, tramadol, hydrocodone and oxycodone can be used for pain instead.
  - Aspirin should not be used unless the patient has a vascular or coronary stent or a prior cerebrovascular accident.
  - Those who need to take aspirin or prednisone must also take a proton pump inhibitor to prevent marginal ulcers.

- Oral bisphosphonates
  - Could present problems due to a reduced pouch size, which may increase the risk of GI ulceration.
  - IV bisphosphonate (zoledronic acid) or denosumab (if bisphosphonate is contraindicated) should be considered as first-line agents.
  - Anabolic agents (teriparatide, abaloparatide, and romosozumab) can be used as second-line agents.

- Extended-release, delayed-release, enteric-coated or film-coated dosage formulations
  - Drug absorption can be reduced due to decreased intestinal length and surface area and these formulations require 2-12 hours for absorption. The reduction in functional intestine length makes it likely that ER preparations have passed through the GI tract before absorption is complete.
  - The immediate-release dosage forms should be used instead which could increase the frequency of daily dosing.
  - A change to a liquid, subcutaneous, intranasal or transdermal medication formulation could increase absorption by eliminating the need for drug dissolution.

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